1-22-75

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 000265

SUBJECT: Request for the establishment of final tolerances for combined negligible residues of the herbicide N-phosphonomethyl glycine (glyphosate) and its metabolite aminomethyl phosphonic acid in or on forage grasses (crop group) and soybean forage and hay at 0.2 ppm; and various crop grains and soybeans at 0.1 ppm.

DATE: 1975

TO: Product Manager

FROM: TB

Pesticide Petition # 5F1536

Trade Name: Roundup

Related petitions: 4G1444, 5G1523, 5G1561, 5F1560

Initial review of the toxicology data was done by R. Landolt in connection with PP# 4G1444 (see memo dated 5-9-74). A summary of these data appears in a memo dated 8-21-74 (R. Landolt, PP# 5G1523) in which TB recommended in favor of establishing the proposed temporary tolerances of 0.2 ppm in or on forage hay and straw of barley, buckwheat, oats, rice, rye and sorghum (milo); and 0.1 ppm in or on grain of barley, buckwheat, oats, rice, rye, and sorghum (milo). In a memo dated 1-23-75, TB (D.M Reisa, PP# 5G1523) recommended in favor of establishing a proposed tolerance of 0.05 ppm in animal liver and kidney. A summary of the data originally reviewed by R. Landolt is attached (Appendix "A"). New submissions which are reviewed below include:

1) a 2-year feeding study in beagle dog (11-30-73)
2) a 2-year feeding study in rats (1-14-74)

TWO-YEAR FEEDING STUDY IN BEAGLE DOGS (Industrial Biotest) (11-30-73)

4 males and 4 females were assigned to the control group and to each of the three experimental groups (30, 100, and 300 ppm). The following parameters were monitored and found not to be significantly different from controls: body weight, food consumption, behavioral reaction, mortality, hematological studies, blood chemistry, urinanalysis, organ weights, gross pathology, histopathology. The following studies were conducted upon each dog from the control

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and experimental groups just prior to the inc[illegible] study and after 3, 6, 9, 12, 18, and 24 months of tes[illegible] and were comparable to controls:

Hematology - WBC, RBC, hematocrit, and differential leukocyte count

Blood Chemistry - BUN, glucose, SAP, SGOT, SGPT

Urinalysis - albumin, glucose, pH, microscopic elements

At the conclusion of the study, the dogs from each group were sacrificed and all major tissues and organs were examined grossly.

Organ Weights - liver, kidneys, heart, brain, spleen, gonads, adrenal glands, thyroid pituitary and testes.

Histology (Craig Fischer, D.V.M., veterinary pathologist)
The following were examined histologically (H&E strain): adrenal glands, aorta (thoracic), bone marrow (sternum), brain (cerebrum, cerebellum, pons), caecumn colon, esophagus, gall bladder, gonads, heart, kidneys, liver, lungs, cervical and mesenteric lymph nodes, skeletal muscle, pancreas, sciatic nerve pituitary, prostate, submaxillary salivary gland, small intestine, spinal cord, spleen, stomach, trachea, thyroid, uterus, urinary bladder. The histological changes in the above tissues were not compound-related and were compatible with lesions normally seen in dogs maintained under laboratory conditions. The NEL for this study is in excess of 300 ppm.

TWO-YEAR FEEDING STUDY IN THE RAT (Industrial Biotest) (1-14-74)

50 male and 50 female rats (Charles River strain) were assigned to the control group and to each of 3 dose levels (30, 100, and 300 ppm). No abnormalities were noted in any of the following parameters which could be attributed to the ingestion of glyphosate: body weights, food consumption, mortality, behavioral reactions, hematology, blood chemistry, urinalysis, gross pathology, and organ weights.

Blood and urine samples were collected individually from five rats of each sex from each group after 3 months of feeding. Samples were collected from 10 rats of each sex from each group after 6, 9, 12, 18, and 24 months of feeding. The following parameters were

monitored and found to be comparable to controls:

Hematology - hematocrit, RBC, WBC, hemoglobin, differential leukocyte count
Blood Chemistry - BUN, SAP, SGPT, fasted blood glucose
Urinalysis - glucose, albumin, pH, specific gravity, microscopic elements

Gross and Histopathology (Ward R. Richter, D.V.M., veterinary pathologist)

Necropsies were performed on all post-mortem animals, on all sacrificed animals and all animals surviving the 24-month test period. Organs weighed at the 24-month sacrifice included the brain, gonads, heart, kidneys, liver, lungs, and spleen.

Histological examination was conducted on 10 males and 10 females each from the control and highest dose level. Tissues and organs examined included: heart, liver, lungs, pancreas, stomach, small intestine, caecum, colon, spleen, lymph nodes, kidney, urinary bladder, testis, seminal vesicle, ovary, prostate, uterus, pituitary, adrenal gland, salivary gland, thyroid, parathyroid, skeletal muscle, bone marrow, peripheral nerve trachea, spinal cord, eye, optic nerve and brain.

Tumors and tissues with signs of possible tumor formation were submitted for histopathological examination and classification. In addition, the livers of animals in all dosage groups were examined, particularly for lipid.

Histological evaluation revealed a treatment-related increase in the incidence, in the degree of lobular involvement, and in the relative amount of lipid in the liver cells of the 300 ppm group. The amount of lipid in the livers of the 30 and 100 ppm groups appeared to be comparable to that of controls.

Tumorigenicity

No compound-related increase in tumor type or number was noted. Those tumors which were found were judged to be normal for rats of this age and strain and appeared in the control group as well as the experimental groups.

The NEL for the 2-year rat study is 100 ppm. The effect at the next highest dose level (300 ppm) is the presence of lipid vacuoles within liver cells.

Recommendation

The data presented in these two chronic studies support the proposed residue tolerances.

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Toxicology Branch
Registration Division

cc: CB, EEEB, Division File, Branch File, PP No. 5F1536
R/D Init: GEWhitmore 1-22-75

Init: GEWhitmore

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Appendix A

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Summary Toxicological Evaluation

Acute Studies

Species	Route	Formulation	LD_{50} or Dose mg/kg	Observations
Rat (M&F)	Oral	Technical	4320 (3930-4750)	Lethargy, diarrhea, weakness collapse. Hemorrhagic lungs and liver. GI inflammation.
Rabbit (M&F)	Oral	Technical	3899 (2836-5092	Hypoactivity in 1 hr to 10 days. Death in 3-11 days.
Rat (M&F)	Oral	30%	4900 (4440-5400)	Same as for technical
Rat (M&F)	Oral	41%	4040 (3660-4460)	Same as for technical
Rabbit (M&F)	Dermal	Technical	>7940	No signs of systemic toxicity

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Species	Route	Formulation	LD_{50} or Dose mg/kg	Observations
Rabbit (M&F)	Dermal	30%	>7940	Hypoactivity
Rat (M&F)	Inhalation (4 hrs)	41%	>12.2 mg/l	No signs of systemic toxicity
Rabbit (M&F)	Skin irritation (24 hr exposure)	Technical	0.5 gm	No-irritating score 0/8
Rabbit (M&F)	Skin irritation (24 hr exposure)	30%	0.5 ml	Mild irritant, score 2.3/8
Rabbit	Eye irritation (24 hr exposure)	Technical	100 mg	Slight irritation max. score 12.6/110 in one hour
Rabbit	Eye irritation (24 hr exposure)	30%	0.1 ml	Severe irritant, max. score 64.3/110 in 7 days. Corneal opacity & ulceration
Rabbit	Eye irritation (15 min. exposure)	30%	0.1 ml	Mild irritation, max. score 16/110 in 1 hr. Normal in 7 days.
	(30 min. exposure)	30%	0.1 ml	Mild irritation, max. score 15.3/110 in 1 hr. Normal in 7 days.
	(15 min. exposure)	5%	0.1 ml	Slight irritation, max. score 12/110 in 1 hr. Normal in 7 days.
	(30 min. exposure)	5%	0.1 ml	Slight irritation, max. score 12.6/110 in 1 hr. Normal in 7 days.
	(24 hr. exposure)	5%		Slight irritation, max. score 11.3/110 in 1 hr. Normal in 7 days.

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Species	Route	Formulation	LD50 or Dose mg/kg	Observations
Rat (M&F)	Oral		8300 (7300-9460	Same as for technical
Rabbit (M&F)	Skin irritation	Moistened with water	0.5 gm	Score 0.0
Rabbit (M&F)	Eye irritation		100 mg	Slight irritant max. score 10/110 in 1 hour.

Subacute Studies

Species	Study	Exposure	Formulation	Observations
Rabbit	Dermal Intact and abraded	Daily 15	Water-based 1.64% (use conc.)	Phonation Red well defined erythema, moderate edema and escharosis. Pustules and hemorrhaging. No deaths Increase in leukocyte count and neutrophils with decreased % lymphocytes
			8.2%(5X use conc)	Same gross and hematologic findings as above with 5/20 deaths.
Human (50)	Repeated patch	15	1:9 dilution of the 30% water-based	This material is not a primary irritant fatiguing or sensitizing agent.
Dog	Feeding	90	Technical at 0, 200, 600 and 2000 ppm	No effect level is greater than 2000 ppm
Rat	Feeding	90	Technical at 0, 200, 600 and 2000 ppm	No effect level is greater than 2000 ppm

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Chronic Studies

Species	Study	Exposure	Formulation	Observation
Mice	Carcinogenic feeding	18 month	Technical at 0, 100, and 300 ppm	Not tumorigenic nor carcinogenic at 300 ppm
Rats	Reproduction feeding		Technical at 0, 30, 100 and 300 ppm	No effect level is greater than 300 ppm

Special Studies

Mutagenic - Mice dominant lethal at maximum tolerated dose of 5 and 10 mg/kg.

Conclusion - No mutagenic effects at the maximum tolerated dose of 10 mg/kg.

Teratogenic Study - Rabbits, two levels of technical material were administered at 10 and 30 mg/kg on days 6 through 18 of gestation.

Conclusion - Not teratogenic at 30 mg/kg

Metabolism - Rabbit, single oral doses of C^{14} phosphonomethyl in doses of 5.7 to 8.8 mg/kg.

Results - More than 90% C^{14} activity cleared within 5 days, with 80% in feces, 7-11% in the urine and less than 1% expired as CO_2. Tissue concentration of carboxyl moiety was liver $\geq$ kidney $\geq$ spleen > heart, muscle and gonads.

Metabolism - Rats, single oral dose of methylene carboxyl, or alpha carbon labeled C^{14} phosphonomethyl glycine at 6.7 mg/kg

Results - Within 48 hours male rats cleared 94-98% of the dose as compared to 82-84% for female rats. By 120 hours, 99% of the dose was cleared by both male and female. The label distribution in the feces is carboxyl > alpha carbon > methylene. Males excreted 15% of the dose in the urine with the remainder recovered in feces. Females excreted 35-40% of the dose in the urine with remainder recovered in feces.

Metabolism - Rats, single oral dose of C^{14} aminomethyl phosphonic acid at 6.7 mg/kg.

Results - Within 120 hours 74% of the dose appeared in the feces, 20% in urine and less than 0.1% expired CO_2. More than 50% of the dose was excreted in the feces within 24 hours.

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Metabolism - Rat, C^{14} labeled N-phosphonomethyl glycine was administered by gastrointubation or intraperitoneal injection at 6.7 mg/kg.

Results - N-phosphonomethyl C^{14} glycine is excreted when administered by either route, in the urine and feces as the parent compound.

Metabolism - Rat dietary levels of phosphonomethyl C^{14} glycine were fed at 1.0, 10 and 100 ppm for 14 days followed by a 10 day withdrawal period.

Results - Excretion in both urine and feces reached a plateau level by the sixth day. Most tissue levels plateaued within 10 days or less. The ingested test material was excreted from the body by apparent first order processes so that the amount excreted was directly proportional to the intake. Upon withdrawal, excretion dropped sharply but plateaued temporarily after four days. This excretory plateau during the withdrawal period was due to the excretion of the mobilized tissue residues which were cleared by the kidney or secreted into the intestine with the bile. The cumulative effect was not localized in a single tissue or organ system and was clearly reversibly bound.